Acupuncture for the treatment of chronic obstructive pulmonary disease (COPD): a protocol of a systematic review

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004590
Article Type:	Protocol
Date Submitted by the Author:	01-Dec-2013
Complete List of Authors:	Choi, Tae-Young; Korea Institute of Oriental Medicine, Jun, Ji Hee; Korea Institute of Oriental Medicine, Choi, Jun-Young; Pusan National University, Scholl of Korean Medicine Kim, Jong-In; Kyung hee University, Lee, Myeong Soo; Korea Institute of Oriental Medicine, Ernst, Edzard; University of Exeter, Complementary Medicine, Peninsula Medical School
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Respiratory medicine
Keywords:	COMPLEMENTARY MEDICINE, Chronic airways disease < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine)

Acupuncture for the treatment of chronic obstructive pulmonary disease (COPD): a protocol of a systematic review

Tae-Young Choi[1], Ji Hee Jun[1], Jun-Young Choi[2], Jong-In Kim [3], Myeong Soo Lee[1], Edzard Ernst[4]

[1] *Medical Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea*

[2]*Scholl of Korean Medicine, Pusan National University, Yangsan, South Korea*

[3] *Department of Acupuncture and Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea*

[4]*Complementary Medicine, Peninsula Medical School, University of Exeter, Exeter, UK*

Short title: A protocol of systematic review of acupuncture for COPD

Correspondence to:
Myeong Soo Lee, PhD
Medical Research Division,
Korea Institute of Oriental Medicine,
Daejeon, 305-811, South Korea
Tel: 82-(0)42-868-9266
Fax: 82-(0)42-863-9464
E-mail: drmslee@gmail.com; mslee@kiom.re.kr

License statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ Open and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

Article focus

- The aim of the proposed systematic review is to analyse randomised trial of acupuncture for chronic obstructive pulmonary disease (COPD).

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence using unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening, data extraction and assessing risk of bias will be conducted independently by two of the authors.
- Our systematic review may pertain to the potential incompleteness of the evidence reviewed including publication and location bias, poor quality of the primary data and poor reporting of results.

Abstract

Introduction: This review aims to evaluate the efficacy of acupuncture in the management of chronic obstructive pulmonary disease (COPD).

Methods and analysis: Thirteen databases will be searched from their inception. These include PubMed, AMED, EMBASE, the Cochrane Library, six Korean medical databases (Korean Studies Information, DBPIA, the Korean Institute of Science and Technology Information, the Research Information Centre for Health Database, KoreaMed, and the Korean National Assembly Library), the China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and the Wanfang Database. Only randomised clinical trials (RCTs) using acupuncture for COPD will be considered. The selection of the studies, data abstraction, and validation will be performed independently by two researchers. Methodological quality will be assessed with Cochrane risk of bias.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide the healthcare practice and policy.

Trial registration number: PROSPERO 2013: CRD42013004824.

Keywords: chronic obstructive pulmonary disease (COPD), acupuncture, systematic review, randomised controlled trials

Introduction

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterised by airflow limitation and the gradual loss of lung function that is not fully reversible.[1] COPD includes emphysema and chronic bronchitis, and the main symptoms include cough and breathlessness. This disease is predominantly caused by smoking.[2] COPD is a serious public health problem; according to the World Health Organization (WHO), an estimated 64 million people worldwide currently suffer from moderate to severe COPD.[3] In fact, the WHO ranked COPD as the fifth leading cause of death worldwide, and it is estimated that COPD will be ranked as third leading cause of death by 2030.[4 5] COPD also places a significant burden on healthcare systems, and a loss in health-related quality of life is observed in many patients.[6] Therefore, appropriate therapies are necessary to address this disease.

Acupuncture is a popular treatment for COPD in China.[7] Proponents argue that acupuncture is effective at relieving symptoms, reducing the incidence of COPD exacerbations, and improving quality of life, and that it is associated with fewer adverse effects than conventional approaches to COPD.[8] However, the reliable evidence is unclear.[9] Therefore, the current review aims at systematically evaluating the evidence from RCTs testing the effectiveness of acupuncture for COPD.

Methods

Study registration

The protocol of this systematic review has been registered on PROSPERO 2013 (registration number: CRD42013004824).[10] This systematic review protocol was conducted and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[11]

Data sources

The following databases were searched from their inception: PubMed, AMED, EMBASE, The Cochrane Library, six Korean Medical Databases (Korean Studies Information, DBPIA, the Korean Institute of Science and Technology Information, the Research Information Centre for Health Database, KoreaMed, and the Korean National Assembly Library), and the China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and Wanfang Database. Articles identified through reference lists of included studies and relevant systematic reviews will be considered for inclusion based on their title. Our search strategy will include main keywords 'acupuncture' and 'chronic obstructive pulmonary disease' (Supplement 1). Study selection will be documented and summarized in a PRISMA compliant flowchart (Figure 1).

Eligibility criteria

Population

We will include populations with a diagnosis of COPD. We only will include studies in which an external set of criteria had been used to screen participants for the condition (e.g., criteria from the Global Initiative for Obstructive Lung Disease (GOLD),[1] American

Thoracic Society (ATS),[12] British Thoracic Society (BTS),[13] or Group of Chronic Obstructive Pulmonary Diseases/the Branch of Respiratory Diseases/Chinese Medical Association [14-16]). Included patients will be those who are clinically stable and do not show evidence of an exacerbation one month prior to study entry. Patients with significant diseases other than COPD, including a diagnosis of asthma, cystic fibrosis, bronchiectasis or other lung diseases, will be excluded.

Interventions

Studies that evaluated any type of invasive acupuncture will be included. The treatments considered have to involve needle insertion at acupuncture points, pain points or trigger points and had to be described as acupuncture. Studies investigating other methods of stimulating acupuncture points without needle insertion (e.g., acupressure, pressed studs, laser stimulation or transcutaneous electrical stimulation) will be excluded. Control interventions in controlled studies may include treatments such as general care, sham treatment (interventions mimicking 'true' acupuncture/true treatment but deviating in at least one aspect considered important by acupuncture theory, such as skin penetration or correct point location), waiting list care, or other treatment (e.g., relaxation, physical therapies). We also will include trials that compared acupuncture plus another active treatment versus that other active treatment alone. Thus, we will include all pragmatic trials that compared acupuncture with any other treatments (e.g., drugs, exercise, education, etc.). Because our objective is to evaluate the effects of acupuncture compared to non-acupuncture controls, we will exclude RCTs in which one form of acupuncture was compared to another form of acupuncture.

Outcome measures

Primary outcomes

1. Treatment efficacy: the number of patients whose COPD symptoms improved

2. Quality of life: measured using a validated questionnaire, e.g., St. George's Respiratory Questionnaire (SGRQ) [17]

Secondary outcomes

1. Pulmonary function: Change in forced expiratory volume in one second (FEV1) and change in forced ventilatory capacity (FVC) [18] (trough, peak and average) and other measures of pulmonary function

2. Dyspnoea using Borg scale score [19]

3. Anxiety on a 10 cm Visual analogue scale (VAS) [20]

4. Exercise tolerance: six-minute walk test [21]

5. Adverse events

Study design

Only RCTs will be included. Observational, cohort, case-control, case series, qualitative studies, uncontrolled trials and laboratory studies were excluded.

Data extraction

All articles will be read by two independent reviewers who extract data from the articles according to predefined criteria. The extracted data will include the authors, year of publication, country, study size, age and gender of the participants, acupuncture intervention, control intervention, main outcomes, and adverse effects. The extracted data will be tabulated

(Supplement 2) for further analysis. Details regarding the acupuncture and control interventions will be extracted on the basis of the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA) [22] (Supplement 3).

Risk of bias assessment

Quality assessment will be performed using the tool for 'risk of bias' from the Cochrane Handbook for Systematic Reviews of Interventions (Supplement 4).[23] The following characteristics will be assessed: (1) Was the allocation sequence adequately generated? (2) Was the allocation adequately concealed? (3) Was knowledge of the allocated interventions adequately presented during the study? (4) Were incomplete outcome data adequately addressed? (5) Were the study reports free of the suggestion of selective outcome reporting? and (6) Was the study free of other problems that could introduce a risk of bias? This review used ‘L, U, and H’ as keys for these judgments; where ‘Low’ (L) indicated a low risk of bias, ‘Unclear’ (U) indicated that the risk of bias was uncertain, and ‘High’ (H) indicated a high risk of bias. Disagreements will be resolved by discussion between all authors.

Data synthesis

All statistical analyses will be conducted using the Cochrane Collaboration’s software program, Review Manager (RevMan), Version 5.1 for Windows (Copenhagen, The Nordic Cochrane Center). Differences between the intervention and control groups will be assessed. In the analysis of clinical efficacy, count data will be assessed in terms of risk ratios (RRs), and continuous data will be assessed in terms of mean difference (MD). Both count data and continuous variables will be expressed as efficacy values with 95% confidence intervals

(CIs). In cases of outcome variables with different scales, the standard mean difference (SMD) will be used instead of the weighted MD (WMD). If the meta-analyses exhibit heterogeneity (defined as results of tests of heterogeneity that indicate that $P < 0.1$ and $I^2 \geq 50\%$), then a random effects model will be used to assess combined efficacy values; otherwise, fixed effects models were used for these assessments. Publication bias will be assessed using funnel plots and Eggers' regression method [24]. If missing data are detected, we will request any missing or incomplete information from the original study investigators. Subgroup analysis will be conducted according to different control interventions, the type of acupuncture, the design of the trial (acupuncture vs. conventional medication, acupuncture combined conventional medication vs. conventional medication), and treatment frequency. Sensitivity analysis will be performed to evaluate the robustness of the meta-analysis results. Consistent with other meta-analyses and meta-regressions,[25] the primary quality measure will be a binary measure of allocation concealment.[26] Therefore, the risk of bias assessment for included studies will be summarised in a table, and the results and implications will be critically discussed.

Discussion

To date, no systematic reviews have examined the use of acupuncture in the treatment of COPD. This systematic review will provide a detailed summary of the current evidence related to the effectiveness of acupuncture in treating the symptoms of patients with COPD. This evidence will be useful to practitioners, patients, and health policy makers regarding the use of acupuncture in COPD treatment.

Acknowledgement

TYC, JHJ and MSL were supported by Korea Institute of Oriental Medicine (K13400 and K13281).

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TYC and MSL conceived the study, developed the criteria and searched the literature, performed data analysis and wrote the protocol. JHJ assisted in searched the Chinese literature, extraction of data. JYC and JIK wrote the introduction of this protocol. EE advised on protocol design and revised the manuscript. All authors read and approved the final manuscript.

Reference

1. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2013. Available at: www.goldcopd.org. Accessed November 2013.

2. National Institute for Health and Care Excellence. Chronic Obstructive Pulmonary Disease (update): full guideline. Available at: http://guidancenice.org.uk/CG101/Guidance/pdf/English. Accessed November 2013.

3. World Health Organization. Chronic obstructive pulmonary disease (COPD). Available at: http://www.who.int/mediacentre/factsheets/fs315/en/index.html. Accessed November 2013.

4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. Lancet 1997;**349**:1498-504

5. World Health Organization. Chronic obstructive pulmonary disease (COPD). Available at: http://www.who.int/respiratory/copd/en/. Accessed November 2013.

6. Menzin J, Boulanger L, Marton J, et al. The economic burden of chronic obstructive pulmonary disease (COPD) in a U.S. Medicare population. Respir Med 2008;**102**(9):1248-56

7. Jiang YL, Wang HF, Li JS. Research comment on the treatment of respiratory failure of acute exacerbation of chronic obstructive pulmonary disease by chinese medicine. China J Chin Med 2012;**27**(169):670-72

8. Suzuki M, Namura K, Ohno Y, et al. Combined standard medication and acupuncture for COPD: a case series. Acupunct Med 2012;**30**(2):96-102

9. Gibson D, Bruton A, White P. Acupuncture for respiratory disorder: what's the point? Expert Rev Respir Med 2010;**4**(1):29-37

10. PROSPERO. PROSPERO International prospective register of systematic reviews Avilable at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID= CRD42013004824

11. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Ann Intern Med 2009;**151**:W-65-W-94

12. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. American Journal of Respiratory and Critical Care Medicine 1995;**152**(5 Pt 2):S77-S121

13. COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52:S7-S15.

14. Branch of Respiratory Diseases/Chinese Medical Association. Diagnostic and therapeutic standards of chronic obstructive pulmonary disease (COPD) (draft). Zhong Hua Jie He He Hu Xi Za Zhi 1997;**20**(4):199-203

15. Group of Chronic Obstructive Pulmonary Disease/Branch of Respiratory Diseases/ Chinese Medical Association. Guidance of diagnosis and treatment of chronic obstructive pulmonary disease. Zhong Hua Jie He He Hu Xi Za Zhi 2002;**25**(8):453-60

16. Group of Chronic Obstructive Pulmonary Disease/Branch of Respiratory Diseases/ Chinese Medical Association. Guidance of diagnosis and treatment of chronic obstructive pulmonary disease (reversed edition in 2007). Zhong Hua Jie He He Hu Xi Za Zhi 2007;**30**(1):8

17. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation: the St George's Respiratory Questionnaire. . Am Rev Respir Dis 1992;**145**(6):1321-27

18. American Thoracic Society. Standardization of spirometry, 1994 update. Am J Respir Crit Care Med 1995;**152**(3):1107-36

19. Borg GA. Psychophysical bases of perceived exertion. Med Sci Sports Exerc 1982;**14**(5):377-81

20. Kindler CH, Harms C, Amsler F, et al. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. Anesth Analg 2000;**90**(3):706-12

21. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. Am J Respir Crit Care Med 2002;**166**(1):111-17

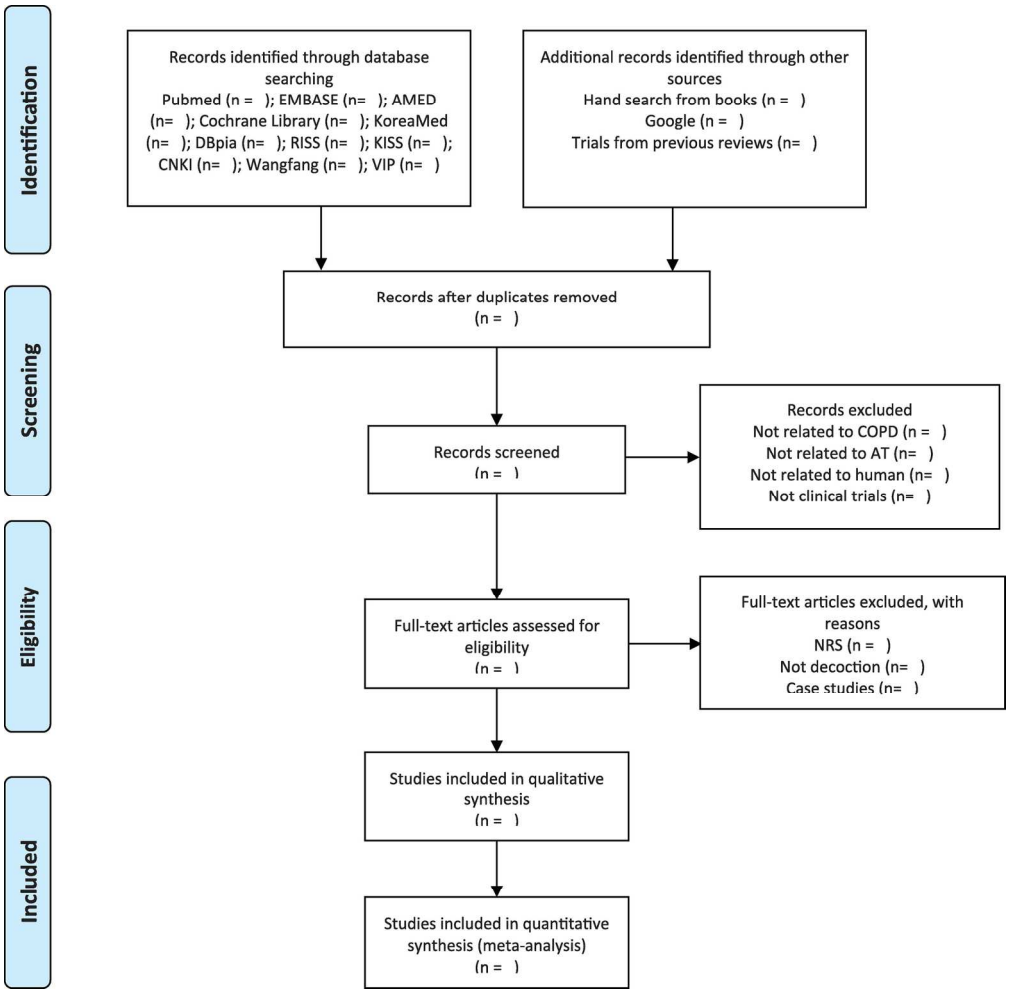
22. MacPherson H, Altman DG, Hammerschlag R. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. PLoS Med 2010;**7**:e1000261

23. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions version 510 (updated March 2011): The Cochrane collaboration.

24. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. BMJ 1997;**315**:629-34

25. Harkness E, MacDonald W, Valderas J, et al. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: a systematic review and meta-analysis. Diabetes Care 2010;**33**(926-930)

26. Hewitt C, Hahn S, Torgerson DJ, et al. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. BMJ 2005;**330**:1057-58



172x169mm (300 x 300 DPI)

Supplement 1. Search strategy

MEDLINE search strategy

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Acupuncture search

1. exp Acupuncture Therapy/

2. exp Medicine, East Asian Traditional/

3. Acupuncture

4. (acupuncture or acupressure or acupoint* or electroacupuncture or electro-acupuncture or meridian* or moxibust* or "traditional chinese medicine" or "traditional oriental medicine").mp. [mp=title, original title, abstract, name of substance word, subject heading word]

5. 4 or 1 or 3 or 2

Filter to identify RCTs

1. exp “clinical trial [publication type]”/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Index Terms

Medical Subject Headings (MeSH)

Acupuncture Therapy [*methods]; Pulmonary Disease, Chronic Obstructive [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

Supplement 2. Summary of randomized clinical studies of acupuncture for COPD.

First author (year) Country	Patients No. (M/F); Age, mean (I/C); Diagnosis; Duration of dieases;	Intervention group (Regime)	Control group (Regime)	Duration of treatment (total times)	Main outcomes	Intergroup differences	Adverse events
Study 1							
Study 2							
Study 3							
……							

COPD: chronic obstructive pulmonary disease

Supplement 3. Summarized acupuncture interventions in the included studies.

First author (year)	Acupuncture Method (Fixed/ Partially Individualized/ Individualized)[1]	Treatment Rationale	Regimen	Acupuncture Points[2]	Response Sought[3]	Co-interventions
Study 1						
Study 2						
Study 3						
……						

1. Acupuncture method was classified into 3 categories on the basis of the levels of individualization: "fixed" means all patients receive the same treatment at all sessions, "partially individualized" means using a fixed set of points to be combined with a set of points to be used flexibly, and "individualized" means each patient receives a unique and evolving diagnosis and treatment.
2. Acupuncture point SI3 refers to 3rd point of small intestine meridian and extra points have different nomenclature (eg, Ex-UE7 means 7th extra point in upper extremity). Ashi points refer to local pain points.
3. De-qi means acupuncture-evoked specific sensations such as soreness, numbness, heaviness, and distention at the site of needle placement, and these sensations may spread to other parts of the body.

Supplement 4. Risk of bias in included RCTs.

First author (year) Country	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Study 1							
Study 2							
Study 3							
……							

L' indicated a low risk of bias; 'U' indicated that the risk of bias is uncertain; 'H' indicated a high risk of bias

BMJ Open

Acupuncture for the treatment of chronic obstructive pulmonary disease (COPD): a protocol of a systematic review

Journal:	*BMJ Open*
Manuscript ID:	bmjopen-2013-004590.R1
Article Type:	Protocol
Date Submitted by the Author:	26-Mar-2014
Complete List of Authors:	Choi, Tae-Young; Korea Institute of Oriental Medicine, Medical Research Division Jun, Ji Hee; Korea Institute of Oriental Medicine, Medical Research Division Choi, Jun-Young; Pusan National University, Department of Korean Medical Science, School of Korean Medicine Kim, Jong-In; Kyung Hee University, Department of Acupuncture and Moxibustion, College of Korean Medicine Lee, Myeong Soo; Korea Institute of Oriental Medicine, Medical Research Division Ernst, Edzard; University of Exeter, Complementary Medicine, Peninsula Medical School
Primary Subject Heading:	Complementary medicine
Secondary Subject Heading:	Complementary medicine, Respiratory medicine
Keywords:	COMPLEMENTARY MEDICINE, Chronic airways disease < THORACIC MEDICINE, RESPIRATORY MEDICINE (see Thoracic Medicine)

Acupuncture for the treatment of chronic obstructive pulmonary disease (COPD): a protocol of a systematic review

Tae-Young Choi[1], Ji Hee Jun[1], Jun-Young Choi[2], Jong-In Kim [3], Myeong Soo Lee[1], Edzard Ernst[4]

[1] *Medical Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea*

[2]*Department of Korean Medical Science, School of Korean Medicine, Pusan National University, Yangsan, South Korea*

[3] *Department of Acupuncture and Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea*

[4]*Complementary Medicine, Peninsula Medical School, University of Exeter, Exeter, UK*

Short title: A protocol of systematic review of acupuncture for COPD

Correspondence to:

Myeong Soo Lee, PhD

Medical Research Division,

Korea Institute of Oriental Medicine,

Daejeon, 305-811, South Korea

Tel: 82-(0)42-868-9266

Fax: 82-(0)42-863-9464

E-mail: drmslee@gmail.com; mslee@kiom.re.kr

License statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ Open and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

Abstract

Introduction: This review aims to evaluate the efficacy of acupuncture in the treatment of chronic obstructive pulmonary disease (COPD).

Methods and analysis: Thirteen databases will be searched from their inception. These include PubMed, AMED, EMBASE, the Cochrane Library, six Korean medical databases (Korean Studies Information, DBPIA, the Korean Institute of Science and Technology Information, the Research Information Centre for Health Database, KoreaMed, and the Korean National Assembly Library), three Chinese Databases (China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and the Wanfang Database). Only randomised clinical trials (RCTs) using acupuncture for COPD will be considered. The selection of the studies, data abstraction, and validation will be performed independently by two researchers. Methodological quality will be assessed with Cochrane risk of bias.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide the healthcare practice and policy.

Trial registration number: PROSPERO 2013: CRD42013004824.

Keywords: chronic obstructive pulmonary disease (COPD), acupuncture, systematic review, randomised controlled trials

Article focus

- The aim of the proposed systematic review is to analyse randomised trial of acupuncture for treating chronic obstructive pulmonary disease (COPD).

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence using unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening, data extraction and assessing risk of bias will be conducted independently by two of the authors.
- Our systematic review may pertain to the potential incompleteness of the evidence reviewed including publication and location bias, poor quality of the primary data and poor reporting of results.

Introduction

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterised by airflow limitation and the gradual loss of lung function that is not fully reversible.[1] COPD includes emphysema and chronic bronchitis, and the main symptoms include cough and breathlessness. This disease is predominantly caused by smoking.[2] COPD is a serious public health problem; according to the World Health Organization (WHO), an estimated 64 million people worldwide currently suffer from moderate to severe COPD.[3] In fact, the WHO ranked COPD as the fifth leading cause of death worldwide, and it is estimated that COPD will be ranked as third leading cause of death by 2030.[4 5] COPD also places a significant burden on healthcare systems, and a loss in health-related quality of life is observed in many patients.[6] Therefore, appropriate therapies are necessary to address this disease.

Description of the intervention

In China, Traditional Chinese Medicine (TCM), as an auxiliary therapy to Western medicine, was extensively employed for the treatment of stable COPD.[7] Acupuncture is a popular treatment for COPD in China.[8] The most common treatment for pain in patients with COPD was acupuncture/ transcutaneous electrical nerve stimulation compared to physiotherapy in the Norwegian general population.[9] Proponents argue that acupuncture is effective at relieving symptoms, reducing the incidence of COPD exacerbations, and improving quality of life, and that it is associated with fewer adverse effects than conventional approaches to COPD.[10]

How the intervention might work

Acupuncture may help relieve COPD that reducing bronchial immune-mediated inflammation[11], and reducing inflammation in general by promoting release of vascular and immunomodulatory factors[12]. However, the reliable evidence is unclear.[13]

Why it is important to this review

Response to treatment may differ with the pathophysiological variation between stable and acute disease. Acute exacerbations of COPD (AECOPD) are defined by acute, excessive increases in dyspnea, cough and/or sputum, and are often associated with bacterial infection, neutrophilic inflammation and specific immune responses.[14]

Objectives

This review aims at systematically evaluating the evidence of acupuncture for treating AECOPD and stable COPD from RCTs.

Methods

Study registration

The protocol of this systematic review has been registered on PROSPERO 2013 (registration number: CRD42013004824).[15] This systematic review protocol was conducted and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[16]

Data sources

The following databases were searched from their inception: PubMed, AMED, EMBASE, The Cochrane Library, six Korean Medical Databases (Korean Studies Information, DBPIA, the Korean Institute of Science and Technology Information, the Research Information Centre for Health Database, KoreaMed, and the Korean National Assembly Library), and the China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and Wanfang Database. Articles identified through reference lists of included studies and relevant systematic reviews will be considered for inclusion based on their title. Our search strategy will include main keywords 'acupuncture' and 'chronic obstructive pulmonary disease' (Supplement 1). Study selection will be documented and summarized in a PRISMA compliant flowchart (Figure 1).

Eligibility criteria

Population

We will include populations with a diagnosis of COPD. We only will include studies in which an external set of criteria had been used to screen participants for the condition (e.g., criteria from the Global Initiative for Obstructive Lung Disease (GOLD),[1] American

Thoracic Society (ATS),[17] British Thoracic Society (BTS),[18] or Group of Chronic Obstructive Pulmonary Diseases/the Branch of Respiratory Diseases/Chinese Medical Association[19-21]). Patients who are clinically stable and do not show evidence of an exacerbation one month prior to study entry will be included. Patients with both stable state and exacerbations of COPD will be included. Patients with significant diseases other than COPD, including a diagnosis of asthma, cystic fibrosis, bronchiectasis or other lung diseases, will be excluded.

Interventions

Studies that evaluated any type of invasive acupuncture will be included. The treatments considered have to involve needle insertion at acupuncture points, pain points or trigger points and had to be described as acupuncture. Studies investigating other methods of stimulating acupuncture points without needle insertion (e.g., acupressure, pressed studs, laser stimulation or transcutaneous electrical stimulation) will be excluded. Control interventions in controlled studies may include treatments such as general care, sham treatment (interventions mimicking 'true' acupuncture/true treatment but deviating in at least one aspect considered important by acupuncture theory, such as skin penetration or correct point location), waiting list care, or other treatment (e.g., relaxation, physical therapies). We also will include trials that compared acupuncture plus another active treatment versus that other active treatment alone. Thus, we will include all pragmatic trials that compared acupuncture with any other treatments (e.g., drugs, exercise, education, etc.). Because our objective is to evaluate the effects of acupuncture compared to non-acupuncture controls, we will exclude RCTs in which one form of acupuncture was compared to another form of acupuncture.

Outcome measures

Primary outcomes

1. Treatment efficacy: the number of patients whose COPD symptoms improved

2. Quality of life: measured using a validated questionnaire, e.g., St. George's Respiratory Questionnaire (SGRQ)[22], Chronic Respiratory Disease Questionnaire (CRQ)[23]

3. Exacerbations[24]: frequency of exacerbations, time to first exacerbation, severity and duration of exacerbations

Secondary outcomes

1. Pulmonary function: Change in forced expiratory volume in one second (FEV1) and change in forced ventilatory capacity (FVC)[25] (trough, peak and average) and other measures of pulmonary function

2. Dyspnoea scores, e.g., Borg scale score[26], a visual analogue scale (VAS)[27], Medical Research Council dyspnoea scale (MRC)[28], components of the COPD assessment test (CAT)[29]

3. Anxiety on a 10 cm VAS[27]

4. Exercise tolerance: e.g., six-minute walk test[30], shuttle walk test[31]

5. Adverse events

6. Participant withdrawal

Study design

Only RCTs will be included. Observational, cohort, case-control, case series, qualitative studies, uncontrolled trials and laboratory studies were excluded.

Data extraction

All articles will be read by two independent reviewers who extract data from the articles according to predefined criteria. The extracted data will include the authors, year of publication, country, study size, age and gender of the participants, acupuncture intervention, control intervention, main outcomes, and adverse effects. The extracted data will be tabulated (Supplement 2) for further analysis. Details regarding the acupuncture and control interventions will be extracted on the basis of the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)[32] (Supplement 3).

Risk of bias assessment

Quality assessment will be performed using the tool for 'risk of bias' from the Cochrane Handbook for Systematic Reviews of Interventions (Supplement 4).[33] The following characteristics will be assessed: (1) Was the allocation sequence adequately generated? (2) Was the allocation adequately concealed? (3) Was knowledge of the allocated interventions adequately presented during the study? (4) Were incomplete outcome data adequately addressed? (5) Were the study reports free of the suggestion of selective outcome reporting? and (6) Was the study free of other problems that could introduce a risk of bias? This review used ‘L, U, and H’ as keys for these judgments; where ‘Low’ (L) indicated a low risk of bias, ‘Unclear’ (U) indicated that the risk of bias was uncertain, and ‘High’ (H) indicated a high risk of bias. Disagreements will be resolved by discussion between all authors.

Data synthesis

All statistical analyses will be conducted using the Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.1 for Windows (Copenhagen, The Nordic Cochrane Center). Differences between the intervention and control groups will be assessed. In the analysis of clinical efficacy, count data will be assessed in terms of risk ratios (RRs), and continuous data will be assessed in terms of mean difference (MD). Both count data and continuous variables will be expressed as efficacy values with 95% confidence intervals (CIs). In cases of outcome variables with different scales, the standard mean difference (SMD) will be used instead of the weighted MD (WMD). If the meta-analyses exhibit heterogeneity (defined as results of tests of heterogeneity that indicate that $P < 0.1$ and $I^2 \geq 50\%$), then a random effects model will be used to assess combined efficacy values; otherwise, fixed effects models were used for these assessments. Publication bias will be assessed using funnel plots and Eggers' regression method.[34] If missing data are detected, we will request any missing or incomplete information from the original study investigators. Subgroup analysis will be conducted according to different control interventions (sham acupuncture vs. conventional medication), the type of acupuncture (Chinese vs Western; standardized acupuncture vs. individually adapted acupuncture points), type of stimulation (manual vs. electric), treatment frequency (less than 14 vs. more than 14), the design of the trial (acupuncture vs. sham acupuncture; acupuncture vs. conventional medication; acupuncture combined conventional medication vs. conventional medication). Sensitivity analysis will be performed to evaluate the robustness of the meta-analysis results. Consistent with other meta-analyses and meta-regressions,[35] the primary quality measure will be a binary measure of allocation concealment.[36] Therefore, the risk of bias assessment for included studies will be summarised in a table, and the results and implications will be critically discussed.

Discussion

To date, no systematic reviews have examined the use of acupuncture in the treatment of COPD. This systematic review will provide a detailed summary of the current evidence related to the effectiveness of acupuncture in treating the symptoms of patients with COPD. This evidence will be useful to practitioners, patients, and health policy makers regarding the use of acupuncture in COPD treatment.

Authors' contributions

TYC and MSL conceived the study, developed the criteria and searched the literature, performed data analysis and wrote the protocol. JHJ assisted in searched the Chinese literature, extraction of data. JYC and JIK wrote the introduction of this protocol. EE advised on protocol design and revised the manuscript. All authors read and approved the final manuscript.

Competing interests

The authors declare that they have no competing interests.

Reference

1. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2013. *Available at: www.goldcopd.org*;[accessed November 2013]

2. National Institute for Health and Care Excellence. Chronic Obstructive Pulmonary Disease (update): full guideline. *Available at: http://guidanceniceorguk/CG101/ Guidance/pdf/English* 2010;[accessed November 2013]

3. World Health Organization. Chronic obstructive pulmonary disease (COPD). *Available at: http://wwwwhoint/mediacentre/factsheets/fs315/en/indexhtml*;[accessed November 2013]

4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349:1498-504

5. World Health Organization. Chronic obstructive pulmonary disease (COPD). *Available at: http://wwwwhoint/respiratory/copd/en/*;[accessed November 2013]

6. Menzin J, Boulanger L, Marton J, et al. The economic burden of chronic obstructive pulmonary disease (COPD) in a U.S. Medicare population. *Respir Med* 2008;102(9):1248-56

7. Guo YM, Tong J, Yao H. Effect of acupuncture on respiratory function of stable chronic obstructive pulmonary disease. *J Guangzhou Uni of Tradit Chin Med* 2013;30(5):658-62

8. Jiang YL, Wang HF, Li JS. Research comment on the treatment of respiratory failure of acute exacerbation of chronic obstructive pulmonary disease by chinese medicine. *China Journal of Chinese Medicine* 2012;27(169):670-72

9. Bentsen SB, Rustøen T, Miaskowski C. Prevalence and characteristics of pain in patients with chronic obstructive pulmonary disease compared to the Norwegian general population. *J Pain* 2011;12(5):539-45

10. Suzuki M, Namura K, Ohno Y, et al. Combined standard medication and acupuncture for COPD: a case series. *Acupunct Med* 2012;30(2):96-102

11. Carneiro ER, Carneiro CR, Castro MA, et al. Effect of electroacupuncture on bronchial asthma induced by ovalbumin in rats. *J Altern Complement Med* 2005;11(1):127-34

12. Zijlstra FJ, van den Berg-de Lange I, Huygen FJ, et al. Anti-inflammatory actions of acupuncture. *Mediators Inflamm* 2003;12(2):59-69

13. Gibson D, Bruton A, White P. Acupuncture for respiratory disorder: what's the point? *Expert Rev Respir Med* 2010;4(1):29-37

14. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176(6):532-55

15. PROSPERO. PROSPERO International prospective register of systematic reviews Avilable at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013004824

16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W-65-W-94

17. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 1995;152(5 Pt 2):S77-S121

18. COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52:S7-S15.

19. Branch of Respiratory Diseases/Chinese Medical Association. Diagnostic and therapeutic standards of chronic obstructive pulmonary disease (COPD) (draft). *Zhong Hua Jie He He Hu Xi Za Zhi* 1997;20(4):199-203

20. Group of Chronic Obstructive Pulmonary Disease/Branch of Respiratory Diseases/ Chinese Medical Association. Guidance of diagnosis and treatment of chronic obstructive pulmonary disease. *Zhong Hua Jie He He Hu Xi Za Zhi* 2002;25(8):453-60

21. Group of Chronic Obstructive Pulmonary Disease/Branch of Respiratory Diseases/ Chinese Medical Association. Guidance of diagnosis and treatment of chronic obstructive pulmonary disease (reversed edition in 2007). *Zhong Hua Jie He He Hu Xi Za Zhi* 2007;30(1):8

22. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation: the St George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145(6):1321-27

23. Schünemann HJ, Puhan M, Goldstein R, et al. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). *COPD* 2005;2(1):81-89

24. Steer J, Gibson GJ, Bourke SC. Predicting outcomes following hospitalization for acute exacerbations of COPD. *QJM* 2010;103(11):817-29

25. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152(3):1107-36

26. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-81

27. Kindler CH, Harms C, Amsler F, et al. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. *Anesth Analg* 2000;90(3):706-12

28. Stenton C. The MRC breathlessness scale. *Occup Med (Lond)* 2008;58(3):226-27

29. Raghavan N, Lam YM, Webb KA, et al. Components of the COPD Assessment Test (CAT) associated with a diagnosis of COPD in a random population sample. *COPD* 2012;9(2):175-83

30. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166(1):111-17

31. Singh SJ, Morgan MD, Scott S, et al. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;47(12):1019-24

32. MacPherson H, Altman DG, Hammerschlag R. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med* 2010;7:e1000261

33. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions version 510 (updated March 2011): The Cochrane collaboration.

34. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34

35. Harkness E, MacDonald W, Valderas J, et al. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33(926-930)

36. Hewitt C, Hahn S, Torgerson DJ, et al. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. . *BMJ* 2005;330:1057-58

Acupuncture for the treatment of chronic obstructive pulmonary disease (COPD): a protocol of a systematic review

Tae-Young Choi[1], Ji Hee Jun[1], Jun-Young Choi[2], Jong-In Kim [3], Myeong Soo Lee[1], Edzard Ernst[4]

[1] *Medical Research Division, Korea Institute of Oriental Medicine, Daejeon, South Korea*

[2]*Department of Korean Medical Science, School of Korean Medicine, Pusan National University, Yangsan, South Korea*

[3] *Department of Acupuncture and Moxibustion, College of Korean Medicine, Kyung Hee University, Seoul, South Korea*

[4]*Complementary Medicine, Peninsula Medical School, University of Exeter, Exeter, UK*

Short title: A protocol of systematic review of acupuncture for COPD

Correspondence to:

Myeong Soo Lee, PhD

Medical Research Division,

Korea Institute of Oriental Medicine,

Daejeon, 305-811, South Korea

Tel: 82-(0)42-868-9266

Fax: 82-(0)42-863-9464

E-mail: drmslee@gmail.com; mslee@kiom.re.kr

License statement

The Corresponding Author has the right to grant on behalf of all authors and does grant on behalf of all authors, an exclusive licence (or non-exclusive for government employees) on a worldwide basis to the BMJ Publishing Group Ltd and its Licensees to permit this article (if accepted) to be published in BMJ Open and any other BMJPGL products to exploit all subsidiary rights, as set out in our licence (http://group.bmj.com/products/journals/instructions-for-authors/licence-forms).

Article focus

- The aim of the proposed systematic review is to analyse randomised trial of acupuncture for treating chronic obstructive pulmonary disease (COPD).

Key messages

- This systematic review will be performed using a comprehensive search strategy and will establish the current status of the evidence using unbiased methods.

Strengths and limitations of this study

- The strength of this systematic review is its extensive, unbiased search of various databases without a language restriction.
- The trial screening, data extraction and assessing risk of bias will be conducted independently by two of the authors.
- Our systematic review may pertain to the potential incompleteness of the evidence reviewed including publication and location bias, poor quality of the primary data and poor reporting of results.

Abstract

Introduction: This review aims to evaluate the efficacy of acupuncture in the treatment of chronic obstructive pulmonary disease (COPD).

Methods and analysis: Thirteen databases will be searched from their inception. These include PubMed, AMED, EMBASE, the Cochrane Library, six Korean medical databases (Korean Studies Information, DBPIA, the Korean Institute of Science and Technology Information, the Research Information Centre for Health Database, KoreaMed, and the Korean National Assembly Library), three Chinese Databases (China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and the Wanfang Database). Only randomised clinical trials (RCTs) using acupuncture for COPD will be considered. The selection of the studies, data abstraction, and validation will be performed independently by two researchers. Methodological quality will be assessed with Cochrane risk of bias.

Dissemination: The systematic review will be published in a peer-reviewed journal. The review will also be disseminated electronically and in print. Updates of the review will be conducted to inform and guide the healthcare practice and policy.

Trial registration number: PROSPERO 2013: CRD42013004824.

Keywords: chronic obstructive pulmonary disease (COPD), acupuncture, systematic review, randomised controlled trials

Introduction

Description of the condition

Chronic obstructive pulmonary disease (COPD) is a slowly progressive disease characterised by airflow limitation and the gradual loss of lung function that is not fully reversible.[1] COPD includes emphysema and chronic bronchitis, and the main symptoms include cough and breathlessness. This disease is predominantly caused by smoking.[2] COPD is a serious public health problem; according to the World Health Organization (WHO), an estimated 64 million people worldwide currently suffer from moderate to severe COPD.[3] In fact, the WHO ranked COPD as the fifth leading cause of death worldwide, and it is estimated that COPD will be ranked as third leading cause of death by 2030.[4 5] COPD also places a significant burden on healthcare systems, and a loss in health-related quality of life is observed in many patients.[6] Therefore, appropriate therapies are necessary to address this disease.

Description of the intervention

In China, Traditional Chinese Medicine (TCM), as an auxiliary therapy to Western medicine, was extensively employed for the treatment of stable COPD.[7] Acupuncture is a popular treatment for COPD in China.[8] The most common treatment for pain in patients with COPD was acupuncture/ transcutaneous electrical nerve stimulation compared to physiotherapy in the Norwegian general population.[9] Proponents argue that acupuncture is effective at relieving symptoms, reducing the incidence of COPD exacerbations, and improving quality of life, and that it is associated with fewer adverse effects than conventional approaches to COPD.[10]

How the intervention might work

Acupuncture may help relieve COPD that reducing bronchial immune-mediated inflammation[11], and reducing inflammation in general by promoting release of vascular and immunomodulatory factors[12]. However, the reliable evidence is unclear.[13]

Why it is important to this review

Response to treatment may differ with the pathophysiological variation between stable and acute disease. Acute exacerbations of COPD (AECOPD) are defined by acute, excessive increases in dyspnea, cough and/or sputum, and are often associated with bacterial infection, neutrophilic inflammation and specific immune responses.[14]

Objectives

This review aims at systematically evaluating the evidence of acupuncture for treating AECOPD and stable COPD from RCTs.

Methods

Study registration

The protocol of this systematic review has been registered on PROSPERO 2013 (registration number: CRD42013004824).[15] This systematic review protocol was conducted and reported using the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement guidelines.[16]

Data sources

The following databases were searched from their inception: PubMed, AMED, EMBASE, The Cochrane Library, six Korean Medical Databases (Korean Studies Information, DBPIA, the Korean Institute of Science and Technology Information, the Research Information Centre for Health Database, KoreaMed, and the Korean National Assembly Library), and the China National Knowledge Infrastructure Database (CNKI), the Chongqing VIP Chinese Science and Technology Periodical Database (VIP), and Wanfang Database. Articles identified through reference lists of included studies and relevant systematic reviews will be considered for inclusion based on their title. Our search strategy will include main keywords 'acupuncture' and 'chronic obstructive pulmonary disease' (Supplement 1). Study selection will be documented and summarized in a PRISMA compliant flowchart (Figure 1).

Eligibility criteria

Population

We will include populations with a diagnosis of COPD. We only will include studies in which an external set of criteria had been used to screen participants for the condition (e.g., criteria from the Global Initiative for Obstructive Lung Disease (GOLD),[1] American

Thoracic Society (ATS),[17] British Thoracic Society (BTS),[18] or Group of Chronic Obstructive Pulmonary Diseases/the Branch of Respiratory Diseases/Chinese Medical Association[19-21]). Patients who are clinically stable and do not show evidence of an exacerbation one month prior to study entry will be included. Patients with both stable state and exacerbations of COPD will be included. Patients with significant diseases other than COPD, including a diagnosis of asthma, cystic fibrosis, bronchiectasis or other lung diseases, will be excluded.

Interventions

Studies that evaluated any type of invasive acupuncture will be included. The treatments considered have to involve needle insertion at acupuncture points, pain points or trigger points and had to be described as acupuncture. Studies investigating other methods of stimulating acupuncture points without needle insertion (e.g., acupressure, pressed studs, laser stimulation or transcutaneous electrical stimulation) will be excluded. Control interventions in controlled studies may include treatments such as general care, sham treatment (interventions mimicking 'true' acupuncture/true treatment but deviating in at least one aspect considered important by acupuncture theory, such as skin penetration or correct point location), waiting list care, or other treatment (e.g., relaxation, physical therapies). We also will include trials that compared acupuncture plus another active treatment versus that other active treatment alone. Thus, we will include all pragmatic trials that compared acupuncture with any other treatments (e.g., drugs, exercise, education, etc.). Because our objective is to evaluate the effects of acupuncture compared to non-acupuncture controls, we will exclude RCTs in which one form of acupuncture was compared to another form of acupuncture.

Outcome measures

Primary outcomes

1. Treatment efficacy: the number of patients whose COPD symptoms improved

2. Quality of life: measured using a validated questionnaire, e.g., St. George's Respiratory Questionnaire (SGRQ)[22], Chronic Respiratory Disease Questionnaire (CRQ)[23]

3. Exacerbations[24]: frequency of exacerbations, time to first exacerbation, severity and duration of exacerbations

Secondary outcomes

1. Pulmonary function: Change in forced expiratory volume in one second (FEV1) and change in forced ventilatory capacity (FVC)[25] (trough, peak and average) and other measures of pulmonary function

2. Dyspnoea scores, e.g., Borg scale score[26], a visual analogue scale (VAS)[27], Medical Research Council dyspnoea scale (MRC)[28], components of the COPD assessment test (CAT)[29]

3. Anxiety on a 10 cm VAS[27]

4. Exercise tolerance: e.g., six-minute walk test[30], shuttle walk test[31]

5. Adverse events

6. Participant withdrawal

Study design

Only RCTs will be included. Observational, cohort, case-control, case series, qualitative studies, uncontrolled trials and laboratory studies were excluded.

Data extraction

All articles will be read by two independent reviewers who extract data from the articles according to predefined criteria. The extracted data will include the authors, year of publication, country, study size, age and gender of the participants, acupuncture intervention, control intervention, main outcomes, and adverse effects. The extracted data will be tabulated (Supplement 2) for further analysis. Details regarding the acupuncture and control interventions will be extracted on the basis of the revised Standards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA)[32] (Supplement 3).

Risk of bias assessment

Quality assessment will be performed using the tool for 'risk of bias' from the Cochrane Handbook for Systematic Reviews of Interventions (Supplement 4).[33] The following characteristics will be assessed: (1) Was the allocation sequence adequately generated? (2) Was the allocation adequately concealed? (3) Was knowledge of the allocated interventions adequately presented during the study? (4) Were incomplete outcome data adequately addressed? (5) Were the study reports free of the suggestion of selective outcome reporting? and (6) Was the study free of other problems that could introduce a risk of bias? This review used ‘L, U, and H’ as keys for these judgments; where ‘Low’ (L) indicated a low risk of bias, ‘Unclear’ (U) indicated that the risk of bias was uncertain, and ‘High’ (H) indicated a high risk of bias. Disagreements will be resolved by discussion between all authors.

Data synthesis

All statistical analyses will be conducted using the Cochrane Collaboration's software program, Review Manager (RevMan), Version 5.1 for Windows (Copenhagen, The Nordic Cochrane Center). Differences between the intervention and control groups will be assessed. In the analysis of clinical efficacy, count data will be assessed in terms of risk ratios (RRs), and continuous data will be assessed in terms of mean difference (MD). Both count data and continuous variables will be expressed as efficacy values with 95% confidence intervals (CIs). In cases of outcome variables with different scales, the standard mean difference (SMD) will be used instead of the weighted MD (WMD). If the meta-analyses exhibit heterogeneity (defined as results of tests of heterogeneity that indicate that $P < 0.1$ and $I^2 \geq 50\%$), then a random effects model will be used to assess combined efficacy values; otherwise, fixed effects models were used for these assessments. Publication bias will be assessed using funnel plots and Eggers' regression method.[34] If missing data are detected, we will request any missing or incomplete information from the original study investigators. Subgroup analysis will be conducted according to different control interventions (sham acupuncture vs. conventional medication), the type of acupuncture (Chinese vs Western; standardized acupuncture vs. individually adapted acupuncture points), type of stimulation (manual vs. electric), treatment frequency (less than 14 vs. more than 14), the design of the trial (acupuncture vs. sham acupuncture; acupuncture vs. conventional medication; acupuncture combined conventional medication vs. conventional medication). Sensitivity analysis will be performed to evaluate the robustness of the meta-analysis results. Consistent with other meta-analyses and meta-regressions,[35] the primary quality measure will be a binary measure of allocation concealment.[36] Therefore, the risk of bias assessment for included studies will be summarised in a table, and the results and implications will be critically discussed.

Discussion

To date, no systematic reviews have examined the use of acupuncture in the treatment of COPD. This systematic review will provide a detailed summary of the current evidence related to the effectiveness of acupuncture in treating the symptoms of patients with COPD. This evidence will be useful to practitioners, patients, and health policy makers regarding the use of acupuncture in COPD treatment.

Competing interests

The authors declare that they have no competing interests.

Authors' contributions

TYC and MSL conceived the study, developed the criteria and searched the literature, performed data analysis and wrote the protocol. JHJ assisted in searched the Chinese literature, extraction of data. JYC and JIK wrote the introduction of this protocol. EE advised on protocol design and revised the manuscript. All authors read and approved the final manuscript.

Reference

1. Global initiative for chronic obstructive lung disease. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: updated 2013. *Available at: www.goldcopd.org*;[accessed November 2013]

2. National Institute for Health and Care Excellence. Chronic Obstructive Pulmonary Disease (update): full guideline. *Available at: http://guidanceniceorguk/CG101/ Guidance/pdf/English* 2010;[accessed November 2013]

3. World Health Organization. Chronic obstructive pulmonary disease (COPD). *Available at: http://wwwwhoint/mediacentre/factsheets/fs315/en/indexhtml*;[accessed November 2013]

4. Murray CJ, Lopez AD. Alternative projections of mortality and disability by cause 1990-2020: Global Burden of Disease Study. *Lancet* 1997;349:1498-504

5. World Health Organization. Chronic obstructive pulmonary disease (COPD). *Available at: http://wwwwhoint/respiratory/copd/en/*;[accessed November 2013]

6. Menzin J, Boulanger L, Marton J, et al. The economic burden of chronic obstructive pulmonary disease (COPD) in a U.S. Medicare population. *Respir Med* 2008;102(9):1248-56

7. Guo YM, Tong J, Yao H. Effect of acupuncture on respiratory function of stable chronic obstructive pulmonary disease. *J Guangzhou Uni of Tradit Chin Med* 2013;30(5):658-62

8. Jiang YL, Wang HF, Li JS. Research comment on the treatment of respiratory failure of acute exacerbation of chronic obstructive pulmonary disease by chinese medicine. *China Journal of Chinese Medicine* 2012;27(169):670-72

9. Bentsen SB, Rustøen T, Miaskowski C. Prevalence and characteristics of pain in patients with chronic obstructive pulmonary disease compared to the Norwegian general population. *J Pain* 2011;12(5):539-45

10. Suzuki M, Namura K, Ohno Y, et al. Combined standard medication and acupuncture for COPD: a case series. *Acupunct Med* 2012;30(2):96-102

11. Carneiro ER, Carneiro CR, Castro MA, et al. Effect of electroacupuncture on bronchial asthma induced by ovalbumin in rats. *J Altern Complement Med* 2005;11(1):127-34

12. Zijlstra FJ, van den Berg-de Lange I, Huygen FJ, et al. Anti-inflammatory actions of acupuncture. *Mediators Inflamm* 2003;12(2):59-69

13. Gibson D, Bruton A, White P. Acupuncture for respiratory disorder: what's the point? *Expert Rev Respir Med* 2010;4(1):29-37

14. Rabe KF, Hurd S, Anzueto A, et al. Global strategy for the diagnosis, management, and prevention of chronic obstructive pulmonary disease: GOLD executive summary. *Am J Respir Crit Care Med* 2007;176(6):532-55

15. PROSPERO. PROSPERO International prospective register of systematic reviews Avilable at: http://www.crd.york.ac.uk/PROSPERO/display_record.asp?ID=CRD42013004824

16. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *Ann Intern Med* 2009;151:W-65-W-94

17. American Thoracic Society. Standards for the diagnosis and care of patients with chronic obstructive pulmonary disease. *American Journal of Respiratory and Critical Care Medicine* 1995;152(5 Pt 2):S77-S121

18. COPD Guidelines Group of the Standards of Care Committee of the BTS. BTS Guidelines for the management of chronic obstructive pulmonary disease. Thorax 1997;52:S7-S15.

19. Branch of Respiratory Diseases/Chinese Medical Association. Diagnostic and therapeutic standards of chronic obstructive pulmonary disease (COPD) (draft). *Zhong Hua Jie He He Hu Xi Za Zhi* 1997;20(4):199-203

20. Group of Chronic Obstructive Pulmonary Disease/Branch of Respiratory Diseases/ Chinese Medical Association. Guidance of diagnosis and treatment of chronic obstructive pulmonary disease. *Zhong Hua Jie He He Hu Xi Za Zhi* 2002;25(8):453-60

21. Group of Chronic Obstructive Pulmonary Disease/Branch of Respiratory Diseases/ Chinese Medical Association. Guidance of diagnosis and treatment of chronic obstructive pulmonary disease (reversed edition in 2007). *Zhong Hua Jie He He Hu Xi Za Zhi* 2007;30(1):8

22. Jones PW, Quirk FH, Baveystock CM, et al. A self-complete measure of health status for chronic airflow limitation: the St George's Respiratory Questionnaire. *Am Rev Respir Dis* 1992;145(6):1321-27

23. Schünemann HJ, Puhan M, Goldstein R, et al. Measurement properties and interpretability of the Chronic respiratory disease questionnaire (CRQ). *COPD* 2005;2(1):81-89

24. Steer J, Gibson GJ, Bourke SC. Predicting outcomes following hospitalization for acute exacerbations of COPD. *QJM* 2010;103(11):817-29

25. American Thoracic Society. Standardization of spirometry, 1994 update. *Am J Respir Crit Care Med* 1995;152(3):1107-36

26. Borg GA. Psychophysical bases of perceived exertion. *Med Sci Sports Exerc* 1982;14(5):377-81

27. Kindler CH, Harms C, Amsler F, et al. The visual analog scale allows effective measurement of preoperative anxiety and detection of patients' anesthetic concerns. *Anesth Analg* 2000;90(3):706-12

28. Stenton C. The MRC breathlessness scale. *Occup Med (Lond)* 2008;58(3):226-27

29. Raghavan N, Lam YM, Webb KA, et al. Components of the COPD Assessment Test (CAT) associated with a diagnosis of COPD in a random population sample. *COPD* 2012;9(2):175-83

30. ATS Committee on Proficiency Standards for Clinical Pulmonary Function Laboratories. ATS statement: guidelines for the six-minute walk test. *Am J Respir Crit Care Med* 2002;166(1):111-17

31. Singh SJ, Morgan MD, Scott S, et al. Development of a shuttle walking test of disability in patients with chronic airways obstruction. *Thorax* 1992;47(12):1019-24

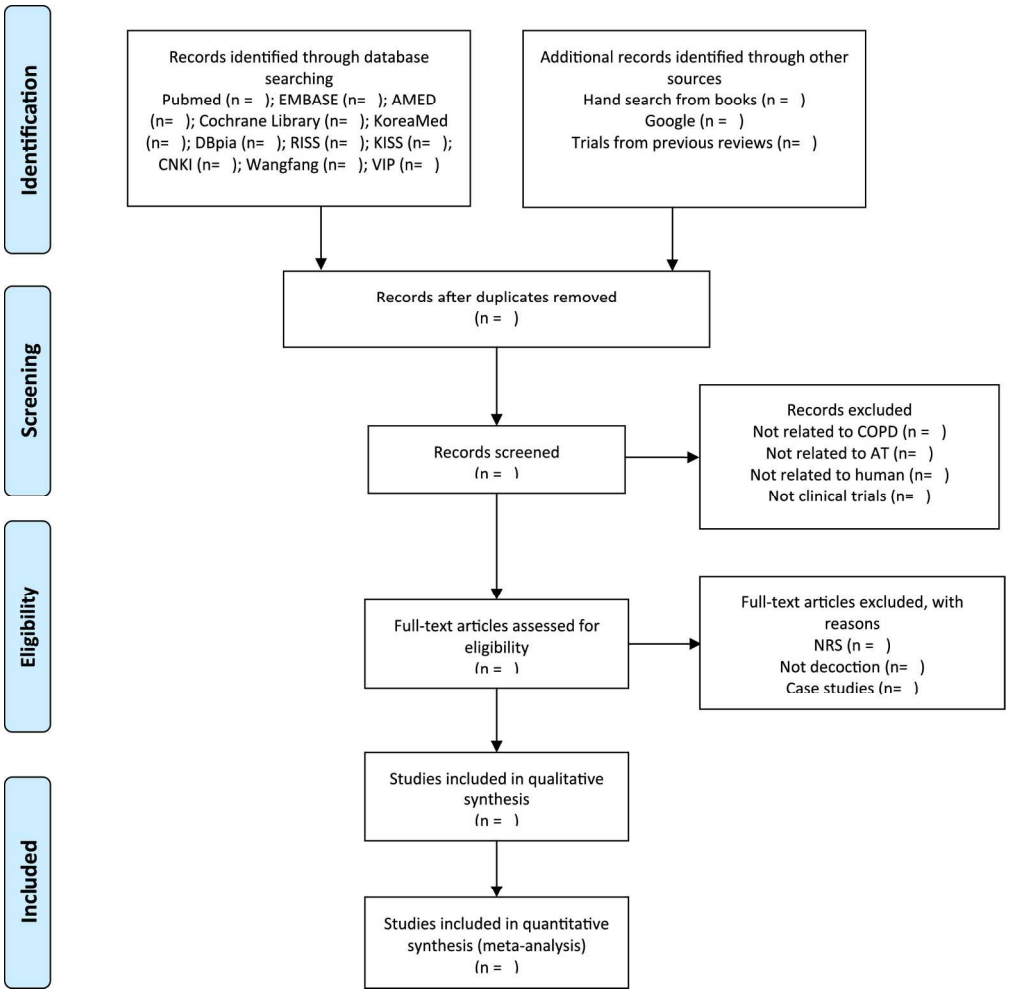
32. MacPherson H, Altman DG, Hammerschlag R. Revised STandards for Reporting Interventions in Clinical Trials of Acupuncture (STRICTA): extending the CONSORT statement. *PLoS Med* 2010;7:e1000261

33. Higgins JPT, Altman DG, Sterne JAC. Chapter 8: Assessing risk of bias in included studies. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions version 510 (updated March 2011): The Cochrane collaboration.

34. Egger M, Davey Smith G, Schneider M, et al. Bias in meta-analysis detected by a simple, graphical test. *BMJ* 1997;315:629-34

35. Harkness E, MacDonald W, Valderas J, et al. Identifying psychosocial interventions that improve both physical and mental health in patients with diabetes: a systematic review and meta-analysis. *Diabetes Care* 2010;33(926-930)

36. Hewitt C, Hahn S, Torgerson DJ, et al. Adequacy and reporting of allocation concealment: review of recent trials published in four general medical journals. . *BMJ* 2005;330:1057-58



176x172mm (300 x 300 DPI)

Supplement 1. Search strategy

MEDLINE search strategy

COPD search

1. Lung Diseases, Obstructive/

2. exp Pulmonary Disease, Chronic Obstructive/

3. emphysema$.mp.

4. (chronic$ adj3 bronchiti$).mp.

5. (obstruct$ adj3 (pulmonary or lung$ or airway$ or airflow$ or bronch$ or respirat$)).mp.

6. COPD.mp.

7. COAD.mp.

8. COBD.mp.

9. AECB.mp.

10. or/1-9

Acupuncture search

1. exp Acupuncture Therapy/

2. exp Medicine, East Asian Traditional/

3. Acupuncture

4. (acupuncture or acupressure or acupoint* or electroacupuncture or electro-acupuncture or meridian* or moxibust* or "traditional chinese medicine" or "traditional oriental medicine").mp. [mp=title, original title, abstract, name of substance word, subject heading word]

5. 4 or 1 or 3 or 2

Filter to identify RCTs

1. exp "clinical trial [publication type]"/

2. (randomised or randomised).ab,ti.

3. placebo.ab,ti.

4. dt.fs.

5. randomly.ab,ti.

6. trial.ab,ti.

7. groups.ab,ti.

8. or/1-7

9. Animals/

10. Humans/

11. 9 not (9 and 10)

12. 8 not 11

The MEDLINE strategy and RCT filter are adapted to identify trials in other electronic databases

Index Terms

Medical Subject Headings (MeSH)

Acupuncture Therapy [*methods]; Pulmonary Disease, Chronic Obstructive [*therapy]; Randomized Controlled Trials as Topic

MeSH check words

Humans

Supplement 2. Summary of randomized clinical studies of acupuncture for COPD.

First author (year) Country	Patients No. (M/F); Age, mean (I/C); Diagnosis; Duration of dieases;	Intervention group (Regime)	Control group (Regime)	Duration of treatment (total times)	Main outcomes	Intergroup differences	Adverse events
Study 1							
Study 2							
Study 3							
……							

COPD: chronic obstructive pulmonary disease

Supplement 3. Summarized acupuncture interventions in the included studies.

First author (year)	Acupuncture Method (Fixed/ Partially Individualized/ Individualized)[1]	Treatment Rationale	Regimen	Acupuncture Points[2]	Response Sought[3]	Co-interventions
Study 1						
Study 2						
Study 3						
……						

1. Acupuncture method was classified into 3 categories on the basis of the levels of individualization: "fixed" means all patients receive the same treatment at all sessions, "partially individualized" means using a fixed set of points to be combined with a set of points to be used flexibly, and "individualized" means each patient receives a unique and evolving diagnosis and treatment.
2. Acupuncture point SI3 refers to 3rd point of small intestine meridian and extra points have different nomenclature (eg, Ex-UE7 means 7th extra point in upper extremity). Ashi points refer to local pain points.
3. De-qi means acupuncture-evoked specific sensations such as soreness, numbness, heaviness, and distention at the site of needle placement, and these sensations may spread to other parts of the body.

Supplement 4. Risk of bias in included RCTs.

First author (year) Country	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias
Study 1							
Study 2							
Study 3							
……							

L' indicated a low risk of bias; 'U' indicated that the risk of bias is uncertain; 'H' indicated a high risk of bias